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Greig Cephalopolysyndactyly Syndrome With Dysgenesis of the Corpus Callosum in a Bedouin Family

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We report on the first known Bedouin family with Greig cephalopolysyndactyly syndrome (MIM 175700). The index patient and his father shared pre- and postaxial polysyndactyly, mild mental retardation, and corpus callosum dysgenesis. Their phenotypic findings were compared with reported cases of both Greig cephalopolysyndactyly (GCPS) and acrocallosal syndromes. This family represents the second report of the rare occurrence of dysgenesis of the corpus callosum in GCPS. © 1996 Wiley-Liss, Inc.

KEY WORDS: Greig cephalopolysyndactyly syndrome, acrocallosal syndrome, corpus callosum hypogenesis, autosomal-dominant inheritance

INTRODUCTION

Greig cephalopolysyndactyly (GCPS) is known to be a fully penetrant autosomal-dominant trait with variable severity of expression [Temtamy and McKusick, 1978; McKusick, 1994]. It involves macrocephaly, frontal prominence, hypertelorism, prominent nasal bridge postaxial polydactyly, occasional preaxial polydactyly and syndactyly of hands, pre- and post axial polydactyly, and syndactyly and polysyndactyly of the toes. It was first described by Greig [1926] in an affected mother and daughter. Since then, several reports have been published describing variable expression of this syndrome [Chudley and Honston, 1982; Baraitser et al., 1983; Tommerup and Nielsen, 1983; Gollop and Fontes, 1985; Kunze and Kaufmann, 1985; Genci and Gencikova, 1986; Winter and Huson, 1988, Pliskin et al. 1988]. Agenesis of the corpus callosum was confirmed in only 1 patient, who was also mildly retarded [Hootnick and Holmes, 1972].

We report on the first known Bedouin family with cephalopolysyndactyly of the Greig type. The index patient and his father both showed severe limb involvement in the form of pre- and postaxial polysyndactyly of the hands and feet, and the rare association of mental retardation and corpus callosum dysgenesis.

CLINICAL REPORTS

Patient 1

The propositus (Fig. 1, V-3) was the second child delivered to nonconsanguineous Bedouin parents. The lack of parental consanguinity was confirmed in spite of the high inbreeding in the father's family. His mother was age 27 years, and the father was age 31 years. Birth weight was 2,400 kg (50th centile), occiptofrontal circumference (OFC) was 36 cm (50th centile), and chest circumference was 29 cm (3rd centile). Apgar scores were 6 and 8 at 1 and 5 min, respectively. Multiple congenital anomalies were recognized at birth. He had a wide anterior fontanelle, short neck, broad high forehead, hypertelorism, board base of the nose, downturned angles of the mouth, umbilical hernia, and glandular hypospadias. He had 27 fingers and toes. The right hand demonstrated preaxial polysyndactyly due to duplication of the thumb, which had double nails. The hand was cupped due to severe complete syndactyly between the medial five digits, while the last digit was separated. The left hand showed preaxial polysyndactyly in the form of bifid thumb with double nails and complete syndactyly of the medial five digits. The sixth digit was separated with a pedunculated postminimus attached to the lateral aspect of middle phalanx of the last digit. The right foot showed varus deformity and seven toes with duplication of the hallux, complete syndactyly of the medial five toes, partial syndactyly between the fifth and sixth toes, separated seventh toe, and well-formed nails. The left foot showed duplication of the hallux with complete syndactyly of the medial five toes, and partial syndactyly between

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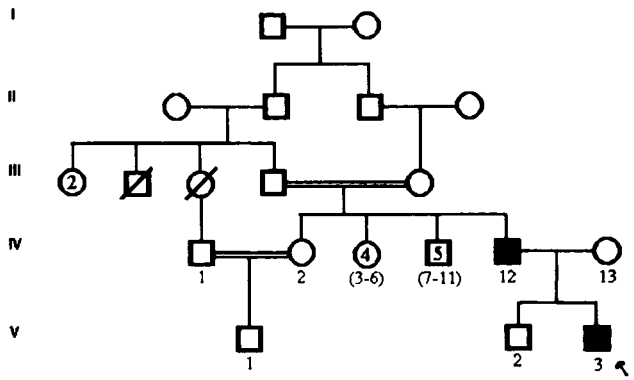

Fig. 1. Pedigree showing index patient and his affected father.

the fifth and sixth toes; the seventh toe was separated, and there was mild varus deformity of the foot. All toes had well-formed nails. Neurological examination showed normal muscle tone and reflexes for age.

Skull roentgenograms confirmed lack of craniosynostosis. Computerized tomography scan of head showed dysgenesis of the corpus callosum (Fig. 2). Chromosome analysis with high-resolution banding showed normal a 46,XY karyotype

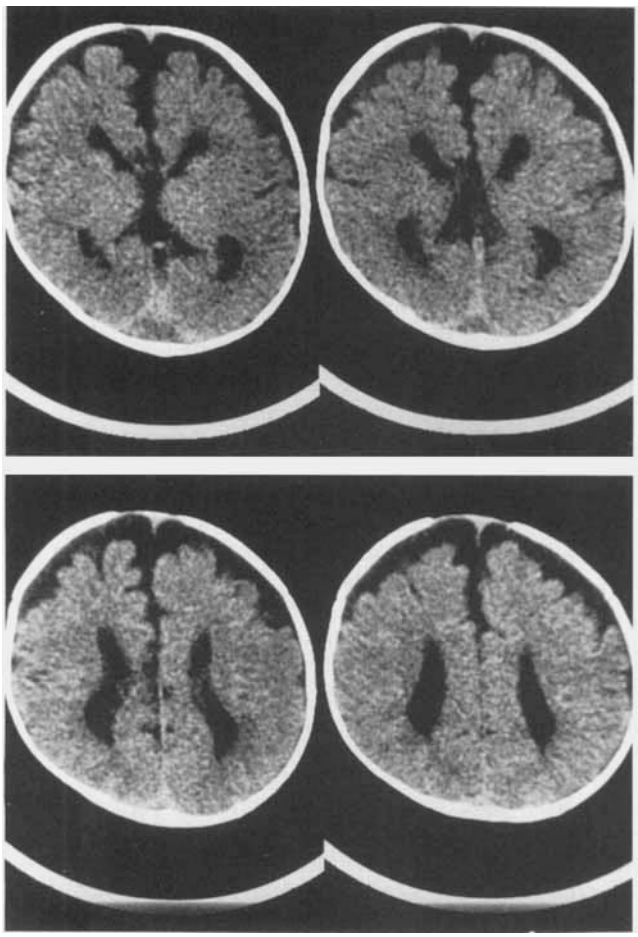

Fig. 2. Computerized tomography scan of head of the proband, showing dysgenesis of corpus callosum, mild dilation of lateral ventricles, and bilateral widening of sylvian fissures with frontoparietal atrophy.

Patient 2

The father (Fig. 1, IV-12) demonstrated a marked similarity of phenotype (Fig. 3). He had macrocephaly (OFC 62.5 cm) >97th centile, high forehead, hypertelorism, bilateral pendular nystagmus, and mild mental retardation (IQ, 65). Both hands showed polysyndactyly with flattened bifid distal phalanges of the thumbs (Fig. 4). Both feet showed polysyndactyly with preaxial polydactyly and complete cutaneous preaxial syndactyly of the toes (Fig. 5).

Computerized tomography scan of the head (Fig. 6) showed dysgenesis of the corpus callosum and other changes similar to those found in his son. Psychiatric assessment showed a modest, shy male with good moral attitude and limited interest, with mild mental retardation and without hearing problems. Psychometric assessment showed that his IQ was 65, and his Minnesota Multiphase Personality Inventory (MMPI) test had no abnormality.

Review of family history showed no similar affected individuals. Chromosome analysis with high-resolution banding showed a 46,XY karyotype. The findings in the index patient and his father are compared with reported data of both GCPS and acrocallosal syndromes (Table I).

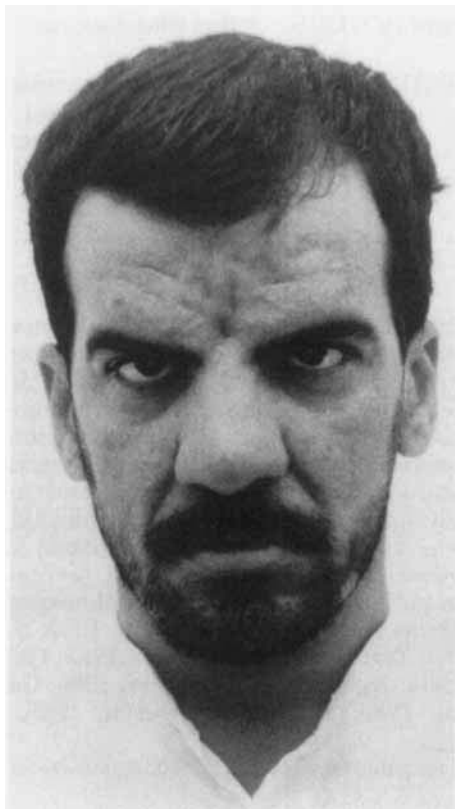

Fig. 3. Photograph of father, showing high forehead and hypertelorism.

Figs. 4 and 5. Post-operative photograph of father's hands, showing bilateral flat, and broad distal phalanges of thumbs, with bifid nails on the left side. The father had bilateral complete cutaneous syndactyly camptodactyly of all digits, and clinodactyly of the little fingers. Photograph of father's legs and feet, showing duplication of halluces with complete cutaneous syndactyly of the medial four toes, and partial syndactyly between the fourth and fifth toes, while the sixth toes were separated.

Fig. 6. Computerized tomography scan of the head of the father, showing dysgenesis of the corpus callosum, mild dilation of lateral ventricles, bilateral widening of the sylvian fissure, and mild frontoparietal atrophy.

DISCUSSION

GCPS syndrome is an autosomal-dominant disorder characterized by macrocephaly, prominent forehead, broad nasal base, mild hypertelorism, and complex polysyndactyly of hands and feet. Mental retardation has been reported in an affected father and his son, the son having agenesis of the corpus callosum, aqueduct stenosis, and communicating hydrocephalus [Hootnick and Holmes, 1972]. Mild degrees of hydrocephaly have also been reported by Baraitser et al. [1983] and Gollep and Fontes [1985]. The genetic locus for GCPS was mapped to 7p13 [Brueton et al., 1988]. DNA analysis of 2 cases of GCPS has further assigned the locus to chromosome 7p12.3 [Wagner et al., 1990, 1992]. Further confirmation of localization to 7p13 occurred when Pettigrew et al. [1991] reported on a de novo interstitial deletion of 7p with breakpoints located at p13 and p14 in an 11-month-old infant with GCPS syndrome, and by Chotai et al. [1994] as a part of molecular study of 6 cases of 7p deletion. A translocation t(3,7)(p21 1,p13) segregating through four generations was found to be invariably associated with GCPS [Tommerup and Nielsen, 1983]. No chromosomal abnormality was observed in the father and son in this report. DNA studies of our patients would be of interest to reveal any submicroscopic alterations. A candidate gene in this region, GLI3, has been found to be disrupted in the translocation cases, and appears to be the gene responsible for GCPS [Vortkamp et al., 1991, 1992].

The findings in our patients are compatible with the diagnosis of GCPS. Acrocallosal syndrome differs from GCPS, as hypotonia and severe mental retardation are two major criteria for the former, while pedunculated postminimus digits together with severe syndactyly of hands and feet are major criteria for the latter. Acrocallosal syndrome is an autosomal-recessive disorder with a wide range of phenotypic expressivity of polysyndactyly [Schinzel and Kaufmann, 1986; Schinzel, 1988; Temtamy and Meguid, 1989; 1989]. The significant phenotypic overlap of these two entities, which share craniofacial abnormalities as well as polysyndactyly, indicates that the two syndromes may be pleiotropic variants of the same mutation, or allelic [Nielson and Thomson, 1982; Schinzel, 1982]. Recently, a linkage analysis using flanking markers did not support this suggestion [Brueton et al., 1992].

TABLE I. Comparison of Major Phenotypic Findings in Bedouin Family With Reported Greig Cephalopolysyndactyly Syndrome and Acrocallosal Syndrome Cases

Manifestations	GCPS[a]	Acrocallosal	Patient 1	Patient 2
MIM (1994)	175700	200990		
Cutaneous syndactyly or partial syndactyly of toes	Frequent, severe	Rare, mild	Severe	Severe
Cutaneous syndactyly of fingers	Frequent, severe	Rare, mild	Severe	Severe
Osseous partial syndactyly	Rare	Absent	–	–
Bifid terminal phalanges of thumb	Present	Rare	+	Severe
Duplication or partial duplication of halluces	Frequent	Frequent	+	+
Postaxial polydactyly of fingers	Frequent	Frequent	+	+
Postaxial polydactyly of toes	Frequent	Frequent	+	–
Hypoplastic or absent corpus callosum	Rare	Major	Dysgenesis	Dysgenesis
Mental retardation	Rare, mild	Major, severe	?	Mild

[a]Modified from Schinzel [1982].

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